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Augmentation of the neuromuscular blocking effects of cisatracurium during desflurane, sevoflurane, isoflurane or total i.v. anaesthesia

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Summary

We have evaluated the enhancement of cisatracurium-induced neuromuscular block by potent inhalation anaesthetic agents, by constructing dose–effect curves for cisatracurium in 84 patients during anaesthesia with 1.5 MAC (70% nitrous oxide) desflurane, sevoflurane, isoflurane or total i.v. anaesthesia (TIVA). Acceleromyography (TOF-Guard) and train-of-four (TOF) stimulation of the ulnar nerve were used (2 Hz every 12 s). Cisatracurium was administered in increments of 15 $\mu g\ kg^{-1}$ until depression of T1/T0 >95% was reached. ANOVA was used for statistical analysis ($\alpha = 0.05$, $\beta = 0.2$). Depression of T1/T0 during potent inhalation anaesthesia was enhanced compared with TIVA. ED_{50} and ED_{95} values of cisatracurium were 15 (SD 5) and 34 (10) $\mu g\ kg^{-1}$ for desflurane; 15 (4) and 32 (7) $\mu g\ kg^{-1}$ for sevoflurane; and 15 (5) and 33 (9) $\mu g\ kg^{-1}$ for isoflurane. These were significantly lower than the values for TIVA (21 (4) and 51 (13) $\mu g\ kg^{-1}$) ($P < 0.01$ in each case). After equi-effective dosing, times to T1/T0 = 25% were similar in all groups (19 (7), 19 (5), 20 (5) *vs* 16 (4) min). Recovery $index_{25–75\%}$ and time to a TOF ration of 0.70 were prolonged significantly by desflurane and sevoflurane compared with TIVA (18 (5), 19 (8) *vs* 12 (4) min and 43 (11), 44 (10) *vs* 35 (5) min, respectively), whereas the difference was not significant for isoflurane (14 (6) and 41 (7) min). (*Br. J. Anaesth*. 1998; **80**: 308–312)

Keywords: neuromuscular block, cisatracurium; neuromuscular block, measurement of response; anaesthetics i.v.; anaesthetics volatile, desflurane; anaesthetics volatile, isoflurane; anaesthetics volatile, sevoflurane

The neuromuscular blocking effect of neuromuscular blocking agents may be enhanced by potent inhalation anaesthetics.[1,2] The magnitude of this effect on the dose–response curve has not been investigated for the recently introduced agent, cisatracurium. This isomer of atracurium is a non-depolarizing neuromuscular blocking agent of the benzylisoquinoline type with fewer side effects than its predecessor, atracurium. The inhalation agents, sevoflurane and desflurane, have a low blood-gas solubility, resulting in rapid uptake and elimination. Their physicochemical properties allow fast recovery thus making both agents suitable for day-case surgery. Underestimation of enhancement of neuromuscular block by potent inhalation agents could result in inadvertent prolongation of block. Therefore, the interaction of cisatracurium with desflurane and sevoflurane was compared with its neuromuscular blocking effects during anaesthesia with isoflurane or total i.v. anaesthesia (TIVA).

Patients and methods

The study was planned in accordance with the recommendations outlined in "Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents".[3] The time required for the first twitch (T1) to recover from 25 to 75% (recovery index) after administration of cisatracurium was mean 9.5 (SEM 1.7) min during halothane anaesthesia in children.[4] Three studies in adults during TIVA reported recovery indices (25–75% recovery of T1/T0) of 17 (SD 5), 17 (SEM 1) or 12.6 (SEM 0.6) min after a single dose of cisatracurium 100 $\mu g\ kg^{-1}$, while recovery time to a train-of-four (TOF) ratio of 0.7 was reported to be 66.7 (SEM 4.9) min.[4–8] If a difference of 20% in potency or recovery time is considered clinically relevant, the calculated sample size would be at least 11 (6–20) patients per group for a single comparison ($\alpha = 0.05$, $\beta = 0.2$; power 80%). As comparison of both desflurane and sevoflurane with TIVA was planned, and as some drop-outs were anticipated, a sample size of 21 patients per group was deemed appropriate.

After obtaining approval from the Ethics Committee and written informed consent, we studied 84 consecutive Caucasian male or female adults (ASA I or II) in a prospective, randomized study. Patients were undergoing minor elective extra-abdominal and extra-thoracic surgery and were free from neuromuscular and endocrine disease. Exclusion criteria were: body weight greater or less than 30% of ideal; patients younger than 18 yr or older than 65 yr; pregnancy or breast feeding; history or laboratory signs of renal (creatinine >100 $\mu mol\ litre^{-1}$) or hepatic (γ-GT >333 $nmol \cdot s^{-1}\ litre^{-1}$) disease; paresis; bedridden patients; medication known to interact with non-depolarizing neuromuscular blocking agents; and allergic diathesis.

Cumulative dose–effect curves for cisatracurium were determined during anaesthesia with 1.5 MAC of desflurane (4.2 vol%), sevoflurane (1.05 vol%) or isoflurane (0.75 vol%) (adjusted for concomitant use of 70% nitrous oxide) and compared with the

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potency determined in patients during total i.v. anaesthesia (TIVA) using propofol–fentanyl. Premedication comprised a benzodiazepine orally on the evening before surgery. Anaesthesia was induced with propofol 2–2.5 mg kg^{-1} and fentanyl 100 μg i.v. in the arm opposite to that connected to the neuromuscular monitoring equipment. Inhalation anaesthetics were administered starting with 2.5–3.0 MAC and the concentration was reduced over the next few minutes to 1.5 MAC. All groups received 70% nitrous oxide in oxygen. End-tidal P_{CO_2} was adjusted to 4.3–4.7 kPa. Body temperature and skin temperature above the monitored muscle were measured and maintained above 35 °C and 32 °C, respectively, by passive warming (wrapping of the patient and arm in a cotton blanket). The arterial pressure cuff was placed on the opposite arm. Light anaesthesia or moderate hypertension (>120% of baseline) was treated initially with fentanyl 100 μg i.v. and, if necessary, by 20% increments of the end-tidal concentration of the inhalation anaesthetic or propofol infusion rate. Hypotension (<80% of baseline) was treated initially by infusion of fluids and then by decreasing by 20% end-tidal concentration of inhalation anaesthetic or propofol infusion rate.

NEUROMUSCULAR MONITORING

The left arm was used for neuromuscular monitoring and was attached to a special arm board (Armboard TOF-Guard, Biometer Int., Odense, Denmark). Neuromuscular monitoring was performed using acceleromyography (AMG) with the piezoelectric ceramic wafer placed at the distal interphalangeal joint of the thumb (TOF-Guard, Biometer Int., Odense, Denmark). Train-of-four (TOF) stimulation of the ulnar nerve via surface stimulating electrodes placed at the wrist was used (supramaximal square wave impulses with 2 Hz, applied every 12 s, 200 μs duration). All data were stored electronically and read out into a computer program for further analysis (TOF-Guard Card Reader 1.0 for Windows, supplied by Organon Teknika, Belgium). Cisatracurium was administered when steady-state conditions were reached (stable control response of AMG for 5 min)[9] and equilibrium of inspiratory and end-tidal concentrations of potent inhalation anaesthetics had occurred, as measured by a Capnomac (Datex).[10] Cumulative increments of cisatracurium 15 μg kg^{-1} were administered repeatedly (injection time <5 s into a fast running i.v. infusion) until depression of the first twitch of at least 95% was achieved.[11] The subsequent dose was administered after at least 4 min and only if three consecutive twitches of identical amplitude were demonstrated (steady state of onset). In addition to depression of the first twitch response, the following variables of neuromuscular block were obtained: duration 25% (time after injection of the last cumulative dose until 25% recovery of T1); recovery index (time to recovery of T1 from 25% to 75%); and interval T1 (25% to a TOF ratio of 0.7). Instead of TOF 0.8 (as suggested by the GCRP guidelines[3]), TOF 0.7 was used as, following our usual clinical practice, in some patients the concentration of inhalation anaesthetic had already been reduced towards the end of operation.

In case of significant baseline shift (defined as failure of T1 to recover to 85–110% with a TOF ratio >0.8), the patient was excluded from further analysis.

CALCULATIONS AND STATISTICAL ANALYSIS

Individual dose–response curves were established by plotting the logarithm of the dose against the logit transform of depression of T1 relative to baseline (100% depression of T1 was adjusted to 99%, 0% to 1%, respectively) using linear least squares regression. After testing for deviation from parallelism, group dose–response curves were established. The ED_{50} and ED_{95} values of cisatracurium were calculated. Data are presented as mean (SD or range). Statistical analysis was performed by one-way ANOVA (Kruskal–Wallis test with post-test; Dunnet's multiple comparison test) using GraphPad Prism 2.0. α was set at 0.05 and β was set at 0.2 (power 80%).

Results

Patients in all groups were similar in age, weight and sex distribution (table 1). Results from six patients were excluded from further analysis (drop-outs)

Table 1 Patient characteristics (mean (SD) [range])

	Sex (M/F)	Weight (kg)	Height (cm)	Age (yr)
Desflurane	12/9	74 (13) [52–98]	174 (10) [174–192]	47 [20–64]
Isoflurane	10/9	75 (12) [54–99]	174 (9) [158–194]	46 [18–63]
Sevoflurane	17/4	76 (13) [50–100]	178 (8) [160–193]	45 [18–65]
TIVA	12/5	76 (15) [54–102]	177 (9) [162–198]	42 [20–64]

Table 2 Depression of T1/T0 after three cumulative doses of cisatracurium 15 μg kg^{-1} during desflurane, isoflurane, sevoflurane and total i.v. anaesthesia (TIVA). ED_{50} and ED_{95} values were calculated after logit transformation (in the 45 μg kg^{-1} column, depression was set at 100% if > 95% was already reached with cisatracurium 30 μg kg^{-1}). In nine of the 17 patients in the TIVA group, a cumulative dose of cisatracurium 60 μg kg^{-1} was given to obtain twitch depression greater than 95%. Mean effect following this dose in the TIVA group was 98 (SD 3) %. Values are mean (SD) [range]. Significant difference compared with TIVA group: * $P < 0.05$, ** $P < 0.01$

	T1/T0 (%)				
	15 μg kg^{-1}	30 μg kg^{-1}	45 μg kg^{-1}	ED_{50} (μg kg^{-1})	ED_{95} (μg kg^{-1})
Desflurane (n=21)	39 (25)*	89 (12)**	98 (3)**	15 (6) [6–24]*	34 (10) [16–56]**
Isoflurane (n=19)	38 (26)*	91 (10)**	98 (4)**	15 (5) [7–24]**	33 (9) [21–55]**
Sevoflurane (n=21)	38 (25)*	91 (9)**	99 (2)**	15 (4) [9–21]**	32 (7) [25–52]**
TIVA (n=17)	14 (16)	71 (18)	92 (7)	21 (4) [13–31]	51 (13) [30–74]

Table 3 Recovery from neuromuscular block during desflurane, isoflurane, sevoflurane and total i.v. anaesthesia after equi-effective doses of cisatracurium (maximal depression of T1/T0 > 95%) (mean (SD) [range]). Significant difference compared with TIVA group: * $P < 0.05$, ** $P < 0.01$

	Duration 25% (min)	Recovery index$_{25-75\%}$ (min)	TOF ratio = 0.70 (min)
Desflurane (n = 21)	19 (6) [11–33]	18 (5) [12–29]**	43 (11) [28–59]*
Isoflurane (n = 19)	20 (4) [13–27]	14 (6) [7–26]	41 (6) [33–54]
Sevoflurane (n = 21)	19 (5) [12–30]	19 (8) [11–40]**	44 (10) [31–65]**
TIVA (n = 17)	16 (4) [8–25]	12 (4) [6–20]	35 (6) [23–42]

because of significant baseline shift ($n = 5$) or reduction of the concentration of the inhalation anaesthetic to less than 1.2 MAC ($n = 1$). In two patients in the isoflurane group and in one in the sevoflurane group, the concentration of inhalation anaesthetic was reduced intermittently to 1.2 MAC during the study because of arterial hypotension. In one patient in each of the inhalation groups the concentration was increased to 1.8 MAC intermittently.

Cisatracurium in cumulative doses led to more pronounced depression of T1 when anaesthesia was maintained with desflurane, sevoflurane or isoflurane compared with the TIVA group (table 2) ($P < 0.01$). To obtain an end-point of T1 of less than 5%, the incremental dose of 15 μg kg^{-1} was administered 2.2 (0.5) (range 1–3), 2.2 (0.5) (2–4) or 2.4 (0.6) (2–4) times in the inhalation anaesthetic groups compared with 3.5 (0.7) (2–5) times in the TIVA group.

The calculated ED_{50} (dose resulting in a 50% effect) and ED_{95} were significantly lower during desflurane (15 (5) and 34 (10) μg kg^{-1}), sevoflurane (15 (4) and 32 (7) μg kg^{-1}) and isoflurane (15 (5) and 33 (9) μg kg^{-1}) anaesthesia compared with the TIVA group (21 (4) and 51 (13) μg kg^{-1}) ($P < 0.01$ in each case) (fig. 1). The dose–response curves were shifted to the left without a significant effect on the slopes compared with TIVA. The degree of potentiation (ratio of ED_{50} during inhalation anaesthesia/ED_{50} during TIVA) was 1.4 for all inhalation anaesthetics.

After equi-effective dosing (e.g. depression of T1/T0 >95%), there were no significant differences in duration 25% for the four groups (19 (7), 19 (5), 20 (5) *vs* 16 (4) min). For desflurane and sevoflurane compared with TIVA, recovery index$_{25-75\%}$ (18 (5), 19 (8) *vs* 12 (4) min) and a TOF ratio of 0.07 (43 (11), 44 (10) *vs* 35 (5) min) were prolonged significantly. There was no significant difference in these variables for isoflurane (14 (6) and 41 (7) min) (table 3).

There were no significant adverse effects attributable to the use of cisatracurium, any of the inhalation anaesthetics or TIVA in any patient.

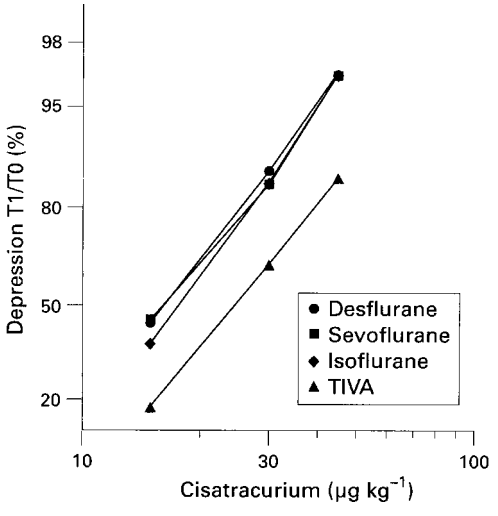

Figure 1 Log–probit plot comparing cumulative bolus dose–response curves for neuromuscular block induced by cisatracurium during desflurane, sevoflurane, isoflurane (1.5 MAC) and total i.v. anaesthesia (TIVA) (depression was set at 100% if >95% was already reached with cisatracurium 30 μg kg^{-1}).

Discussion

The aim of this study was to determine the influence of the inhalation anaesthetics, desflurane and sevoflurane, on the dose–response relationship and pharmacodynamic profile of cisatracurium. The results were compared with those obtained after total i.v. anaesthesia (TIVA). In this study the neuromuscular blocking effect of cisatracurium was enhanced by desflurane, sevoflurane and isoflurane to a similar extent.

POTENCY (AUGMENTATION OF DEPRESSION OF T1/T0)

The cumulative dose technique may underestimate the potency of neuromuscular blocking agents. However, administration of cisatracurium was standardized and the use of potent inhalation anaesthetics or TIVA was randomized; thus the cumulative pattern of cisatracurium administration would have similar effects in all groups. The aim of our study was to determine the anaesthesia-related effects of cisatracurium and not to provide absolute potency data. Nevertheless, the ED_{95} obtained in the present study (51 μg kg^{-1} in the TIVA group) is in accordance with results reported by others (48 μg kg^{-1}, 53 μg kg^{-1}).[8 12]

Using a continuous infusion technique of cisatracurium, Oyos and co-workers reported (in a small number of patients; 14 in four groups) 30–40% reduction in infusion rate required to maintain approximately 95% T1/T0 suppression during enflurane–nitrous oxide and isoflurane–nitrous oxide compared with propofol–nitrous oxide or fentanyl–nitrous oxide anaesthesia.[13] Their data are similar to ours using a cumulative dosing technique during desflurane, sevoflurane and isoflurane anaesthesia. The degree of potentiation found in our study is also in accordance with that reported for other neuromuscular blocking drugs such as rocuronium (factor 1.25–1.4).[14] In theory, assuming that neuromuscular block becomes apparent at 70–75% receptor occupancy and is half maximal at 87.5% receptor occupancy, the ratio ED_{95}/ED_{50} should be 1.95. Our results demonstrated that this holds approximately true for cisatracurium during four different anaesthetic techniques (2.26, 2.13, 2.2 and 2.4). Similar results have been obtained for rocuronium (2.06, 2.0, 1.75 and 1.92).[15]

We started our measurements approximately 10–15 min after induction of anaesthesia. Accelerometric monitoring has been shown to result in stable effects after an equilibration period of 10 min or less.[9] Inspiratory and end-tidal concentrations of each inhalation agent also indicated that steady state was approached. Diffusion of the inhaled anaesthetics into the muscle compartment is slow and requires approximately 30–45 min to approach equilibration. Recent studies indicated that a constant uptake process for desflurane and isoflurane may even continue for more than 1 h.[16] Therefore, in our study this process was probably not complete. Enhancement of neuromuscular block might still increase after more than 1 h of anaesthesia with potent inhalation agents.[17–20] Studies beyond this period are difficult to accomplish and bear little relevance to the routine clinical use of these agents.[21] Typical clinical practice is to administer the first dose of neuromuscular blocking agent soon after induction and before stable anaesthesia has been achieved. Nevertheless, because of the difference in physicochemical properties, equilibration between the muscle compartment and end-tidal concentration is faster for desflurane and sevoflurane than for isoflurane.[22 23] This phenomenon could explain the less pronounced effects of isoflurane on duration and recovery in this study.

DURATION AND RECOVERY

Duration and recovery depend on the dose of the neuromuscular blocking agent.[2 8 24] The most probable reason for the longer duration of action observed in some studies compared with our results is that cisatracurium was given in higher doses (e.g. duration 25% of 46.6 (8) min after 150 $\mu g\ kg^{-1}$ or 68.3 (2.4) min after 200 $\mu g\ kg^{-1}$).[8 12] Furthermore, in our study the total dose was given in increments and therefore recovery from the first dose could have started while the last dose was being administered. This could result in underestimation of duration of action, particularly during the TIVA technique.

Mean recovery $index_{25–75\%}$ was 11.9 min in the TIVA group, in accordance with data obtained during previous investigations with barbiturate–opioid–nitrous oxide anaesthesia after a dose of 100 $\mu g\ kg^{-1}$ (8 min[12] and 12.6 min[8]).

In summary, interaction of cisatracurium and potent inhalation anaesthetics results in potentiation of depression of T1/T0 and a leftward shift in the dose–response relationship. We used repetitive incremental dosing until 95% depression of the first twitch (end-point) was obtained in an individual patient (equi-effective dose). Using this approach of equi-effective dosing, potentiation was demonstrated in terms of ED_{50} and ED_{95} for all inhalation anaesthetics, whereas prolongation of duration of neuromuscular block was less pronounced. In contrast, if neuromuscular blocking drugs are given in identical fixed doses, regardless of the individual effective dose, differences in duration of action become more evident.

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